UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/369,941	08/06/1999	CHARLOTTE A. KENSIL	106941.181	7453

7590 01/31/2003

PENNIE & EDMONDS LLP
1155 AVENUE OF THE AMERICA'S
NEW YORK, NY 10036-2711

EXAMINER
WILSON, MICHAEL C

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 01/31/2003

31

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/369,941	Applicant(s) Kensil
	Examiner Michael C. Wilson	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *9-17-02 and 10-31-02*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *19-28, 63-78, 80-83, and 90-116* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *19-28, 63-78, 80-83, and 90-116* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 26
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10-31-02, paper number 29, has been entered in view of the petition to revive filed 10-31-02, paper number 28. The petition was granted 1-20-02, paper number 30.

The amendment filed 9-17-02, paper number 25, has been entered as requested. Applicant's arguments filed therein have been fully considered but they are not persuasive. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The application number on applicants' response filed 9-17-02 is incorrect. The correct number is 09/369,941.

In exhibit B, claim 19 is incorrect. Item a) in pending claim 19 is limited to "a saponin adjuvant" as in the amendment filed 1-18-02, not "a saponin immunostimulatory adjuvant" as in exhibit B in the response filed 9-17-02. Claim 19 was not amended in the response filed 9-17-02.

Claims 49-61, 79 and 84-89 have been canceled. Claims 90-116 have been added. Claims 19-28, 63-78, 80-83 and 90-116 are pending and under consideration in the instant office action

as they relate to a composition comprising a) saponin and b) an immunostimulatory oligonucleotide, and to a method of using such a composition (Group II). The claims are not being examined as they relate to a composition comprising a) saponin, b) an immunostimulatory oligonucleotide, and c) an antigen, or methods of using such a composition. For examination purposes a "nucleic acid sequence encoding an antigen" is not an antigen because antigens are proteins, and because nucleic acid sequences are materially distinct and separate than proteins.

Specification

The objection to the amendment filed 1-18-02 under 35 U.S.C. 132 because it introduces new matter into the disclosure is withdrawn because "5'X_1CG$X_2$3' on pg 8, line 19-22, and in claims 27 and 57 as originally filed, is 4 nucleotides in length.

Claim Rejections - 35 USC § 112

The rejection of claims 73 and 74 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is withdrawn because "5'X_1CG$X_2$3' on pg 8, line 19-22, and in claims 27 and 57 as originally filed, is 4 nucleotides in length.

1. Claims 19-28, 63-78, 80-83 and 90-116 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The phrase "non-traditional nucleotides" is new matter (claim 25, 26, 65, 66, 96, 97, 109 and 110). Pg 9, 5 lines from the bottom, states the "oligonucleotides may contain... ...linkages in which the nucleotides of the 5' end and/or 3' end... ...have been replaced with any number of non-traditional bases or chemical groups, such as phosphorothioate-modified nucleotides." Thus, the specification describes phosphorothioate-modified nucleotides as chemically modified nucleotides and not as "non-traditional bases." In addition, the specification is limited to oligonucleotides having nucleotides of the 5' end and/or 3' end being "non-traditional nucleotides" which is a different scope than oligonucleotides having any "non-traditional nucleotides" as newly claimed. In addition, the metes and bounds of "non-traditional nucleotides" is unclear (see 112/2nd below).

The phrase "saponin immunostimulatory adjuvant" is new matter (claims 63, 65, 69, 71, 73, 75, 103). Pg 6, lines 8-17, teaches measuring the adjuvant activity of saponin and does not suggest the genus of "saponin immunostimulatory adjuvant" or define the metes and bounds of such saponins. As such, the phrase is new matter.

The phrase "antigen to which an immune response is desired" is new matter (64, 67, 68, 74, 76, 90, 103). Pg 14, lines 22, suggest antigens suitable for enhanced immune response include antigens derived from viruses, bacteria, protozoans, etc. The scope of the antigens claimed is different than the scope of the antigens on pg 14, line 22, because the antigens on pg 14 are for

"enhanced" immune response which is not in the claim. The specification does not suggest which antigens are "desired" as newly claimed. The claim is not limited to viral, bacterial, or protozoan antigens as suggested in the specification. In addition, an immune response to viral antigens is sometimes not desired. For example in gene therapy using adenovirus, it would not be desirable to induce an immune response against adenoviral antigens and destroy the adenovirus. As such, the scope of antigens claimed does not have support in the specification as originally filed.

The phrase "an individual or test system to which a nucleic acid encoding the antigen is administered" is new matter. Support for the phrase cannot be found and has not been provided. Pg 3, lines 13-15, teaches an immunostimulatory oligonucleotide, a saponin and an antigen and does not support administering a nucleic acid sequence encoding an antigen.

The specification does not support administering a nucleic acid sequence encoding an antigen as newly claimed (claims 64, 67, 68, 70, 72, 74, 76, 80, 90 and 103). Pg 14, line 22, through pg 15, line 4, teach that the antigens suitable for the enhanced immune response (pg 14, line 22) may be a nucleic acid encoding the antigen (pg 15, line 1). The "immune response" on pg 14, line 22, refers to the immune response against an antigen in an individual or test system. The citation does not state the nucleic acid sequence is administered to the individual or test system or that the nucleic acid sequences suitable for the enhanced immune response are suitable for putting into the immune adjuvant and administering to an individual or test system. The citation merely states the immune response in the individual or test system may be against a nucleic acid sequence encoding an antigen. For example, tumor cell lines are genetically altered to artificially express

antigens. The immune response in the individual or test system may be directed toward such antigens. The specification does not contemplate combining an immunostimulatory oligonucleotide, a saponin and a nucleic acid sequence encoding an antigen as newly claimed.

The phrase "non-traditional saponin" is new matter. Pg 11, lines 12-17, does not teach the term "non-traditional" and merely contemplates chemically modified saponin comprising at least QS-17, -18, -21, -21-V1 or -21-V2. The specification does not state chemically modified saponins are "non-traditional" as newly claimed. The phrase encompasses a scope than "chemically modified saponins" as originally contemplated; therefore, the phrase is new matter. In addition, the phrase is indefinite (see 112/2nd below).

The phrase "an effective amount of an immune adjuvant" in claim 90 is new matter. No support for the limitation has been provided and none can be found.

The phrase "wherein the nucleic acid encoding the antigen is administering to the individual or test system within 0-2 days of the administration of the immune adjuvant composition" is new matter (claim 113). Pg 18, line 9, contemplates administering saponin and an immunostimulatory oligonucleotide together or separately "within a short period of time (i.e. 0-2 days)." The specification does not contemplate administering DNA encoding an antigen and a mixture of saponin and immunostimulatory oligonucleotide together or separately. One of skill cannot extrapolate administering C and A+B together or separately as newly claimed from administering A and B together or separately as taught in the specification as originally filed. Therefore, the phrase is new matter.

Claims 115-116 are new matter. The specification does not contemplate administering anything before or after a mixture of saponin and immunostimulatory oligonucleotides as newly claimed. Support is not found on pg 18, line 9, which is generic to "within two days."

2. Claims 19-28, 63-78, 80-83 and 90-116 remain rejected and claims 113-116 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing an immune response in an individual comprising administering i) a vector comprising a nucleic acid sequence encoding an antigen operatively linked to a promoter; and ii) a nucleic acid sequence comprising at least one unmethylated CpG to said individual such that an immune response against said antigen occurs in the individual, does not reasonably provide enablement for merely administering a saponin and a nucleic acid sequence comprising at least one unmethylated CpG without also administering a nucleic acid sequence encoding an antigen. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims for reasons of record.

The specification does not enable merely administering saponin and an immunostimulatory oligonucleotide as claimed without a nucleic acid sequence encoding an antigen because the specification does not provide an enabled use for merely administering two adjuvants and because such a composition would induce a non-specific immune response. Applicants argue merely administering two adjuvants can be used to increase the immune response against an antigen administered at a different or at the same time. Applicants argument is not persuasive. The

claims do not require administering antigen at the same time or at a different time. And if they did, such claims would not be examined because they would be directed toward a non-elected invention. The basis of the rejection is that administering two adjuvants as claimed without administering antigen or DNA encoding antigen is not enabled.

Applicants argue the claims have been amended to recite that an antigen encoded by a nucleic acid is also administered to the individual or test system (pg 9 of response). The sentence is unclear. It cannot be determined whether applicants believe that the claim as newly amended requires administering an antigen (i.e. protein) or a nucleic acid sequence encoding the antigen. It is assumed that applicants believe the claims as amended require administering a nucleic acid sequence encoding an antigen because the claims are not being examined as they relate to administering an antigen (see restriction requirement). Applicants argument is not persuasive. Claim 64, for example, is drawn to "a method for increasing the immune response to an antigen to which an immune response is desired in an individual or a test system to which a nucleic acid encoding the antigen is administered comprising administering an effective amount of an immune adjuvant composition of claim 63." The adjuvant composition of claim 63 does not require a nucleic acid sequence encoding an antigen. Claim 64, drawn to a method of administering the composition does not require administering a nucleic acid sequence encoding an antigen. The phrase "to which a nucleic acid encoding the antigen is administered" does not make sense and is an intended use which may not occur.

3. Claims 19-28, 63-78, 80-83 and 90-116 are rejected and claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "immunostimulatory oligonucleotide having an unmethylated CpG" (claim 19, 24, 25, 27, 63, 65, 69, 71, 73, 75, 95, 96, 98, 103, , 108, 109, 111) remains indefinite as the metes and bounds of the oligonucleotides excluded by the claims cannot be determined. The specification defines an "immunostimulatory oligonucleotide comprising at least one unmethylated CpG motif" as an oligonucleotide that activates the immune system (page 8, line 9). The specification states the oligonucleotide may be 4-40 base pairs in length or part of a vector. It is clear that the term is not limited to nucleic acid sequences of a particular size because it may be 4 base pairs in length or part of a vector. It is clear that the term encompasses any nucleic acid sequence having an unmethylated CpG. It is also clear that unmethylated CpG is recognized as foreign and inherently causes an immune response. As such, it appears that any nucleic acid sequence having an unmethylated CpG of any length is encompassed by the claim. What is unclear is what nucleic acids having an unmethylated CpG are excluded from the claims.

The metes and bounds of "non-traditional nucleotides" is indefinite (claim 25, 26, 65, 66, 96, 97, 109 and 110). Pg 9, 5 lines from the bottom, states the "oligonucleotides may contain... ...linkages in which the nucleotides of the 5' end and/or 3' end... ...have been replaced with any number of non-traditional bases or chemical groups, such as phosphorothioate-modified nucleotides." The specification describes replacing nucleotides with chemical groups, such as

phosphorothioate-modified nucleotides, and does not describe "non-traditional bases" as including phosphorothioate-modified nucleotides. The term "non-traditional nucleotides" is not defined in the specification and does not have an art recognized meaning. It is unclear if nicked DNA in which the nucleotides have broken phosphorothioate linkages are encompassed by the term. It is unclear if uracil, a naturally occurring nucleotide which can unnaturally occur in oligonucleotides, is encompassed by the term. As such, the metes and bounds of the phrase cannot be determined.

The metes and bounds of an "antigen to which an immune response is desired" cannot be determined (64, 67, 68, 74, 76, 90, 103). The specification does not define such antigens and the art at the time of filing does not define such antigens. Such antigens are relative because in some circumstances an immune response is desired against a particular antigen while in others circumstances it is not. In addition, the "desire" of one person in the skill may not be the same as another. As such, it is unclear if the phrase limits the antigens encompassed by the claim or limits the circumstances where an immune response is required. If the phrase limits the antigens encompassed by the claim, it is unclear which antigens are excluded. If the phrase does not limit the antigens, but instead limits the circumstances under which an immune response to the antigen is "desired", such circumstances cannot be determined.

The metes and bounds of a "saponin immunostimulatory adjuvant" cannot be determined (claims 63, 65, 69, 71, 73, 75, 103). Applicants have inserted the term "immunostimulatory" in an attempt to distinguish the saponin of Agrawal from the saponin used in the instant invention because the purpose of Agrawal is to decrease the immunostimulatory effect of an oligonucleotide

while the purpose of the instant invention is to cause an immunostimulatory effect using an oligonucleotide. However, the specification does not teach which saponins are "immunostimulatory" or not "immunostimulatory." Nor does the art at the time of filing distinguish between "immunostimulatory" and "non-immunostimulatory" saponins. It is also unclear if any stimulation of the immune response is considered "immunostimulatory" or if it is limited to a particular level or type of immune response. Therefore, one of skill in the art at the time of filing would not have been able to distinguish which saponins were encompassed by the claims.

As amended, the preamble of claims 64, 67, 68, 70, 72, 74, 76 and 90 is unclear. The phrase "...increasing the immune response to an antigen to which an immune response is desired in an individual or a test system" is unclear because it is unclear if the immune response is "desired" or "increasing". The phrase "to which a nucleic acid encoding the antigen is administered" is unclear because the body of the claim does not require administering a nucleic acid sequence encoding the antigen. As such, it is unclear if the nucleic acid sequence is required as part of the composition, administered separately or is an intended use and not required at all. In addition, "a nucleic acid" is one nucleotide which does not encode an antigen as claimed. "A nucleic acid" should be "a nucleic acid sequence". Finally, it is unclear whether the phrase "to which a nucleic acid... ...is administered" refers to just the test system or to either the individual or the test system.

The phrase "non-traditional saponin" (claims 75, 77) is indefinite. The metes and bounds of saponins encompassed by the term cannot be determined. It is unclear if "non-traditional" saponins are modified by the hand of man, or if they are naturally occurring saponins that are purified. If the phrase is intended to embrace saponins that are chemically altered, it is unclear which chemical alterations are "non-traditional." If the phrase is intended to embrace saponins that are purified, it is unclear which saponins are excluded because all saponin is purified from *Quillaja saponiaria*. The specification does not define "non-traditional saponin" and the term did not have an art accepted meaning at the time of filing. On pg 11, lines 12-17, applicants contemplate chemically modified saponins. However, it is unclear that "non-traditional saponins" are limited to chemically modified saponins, purified saponins, or both.

Claim 80 is indefinite because antigens are not encoded by a single "nucleic acid" as claimed. They are encoded by a nucleic acid sequence.

Claim 80 is indefinite because the nucleic acid is not administered in claim 19. It is unclear if applicants intend the claim to be a product by process or if the limitation is intended to limit the immune adjuvants to those having a particular function. If the phrase is intende to be functional language describing the immune adjuvant, it is unclear how "an antigen" in claim 80 correlate to the antigen in claim 19. It is unclear if "a nucleic acid" in claim 80 refers to the DNA vaccine vector in claim 19 or some other nucleic acid. It is also unclear whether "when administered to an individual" refers to administering the immune adjuvant alone or to administering the immune adjuvant and the nucleic acid. If the phrase is intended to refer to administering the immune

adjuvant and the nucleic acid, neither claim 19 or 80 clearly set forth the composition comprises a nucleic acid encoding an antigen.

It is unclear if "a nucleic acid" in claim 90 refers to the DNA vaccine vector in claim 19 or some other nucleic acid.

Claim 90 is indefinite because it does not clearly refer back to the immune adjuvant composition of claim 19. The phase "an immune adjuvant composition" should be --the immune adjuvant composition--.

The metes and bounds of "an effective amount" of the immune adjuvant of claim 19 cannot be determined (claim 90). The amount of such an adjuvant is not defined in the specification or in the art at the time of filing. The effect is not defined in the specification or in the art at the time of filing. It is unclear if the adjuvant must induce an immune response, and if so, how much and what kind of immune response. Since applicants argue some saponins do not cause as great an immune response as others, the metes and bounds of what applicants consider "effective" cannot be determined.

The phrase "and the nucleotide sequence is operatively linked to a promoter" is unclear (claim 103). It is unclear whether it refers to the "nucleotide sequence" in line 8 or in line 5. If applicants are attempting to define the structure of the nucleotide sequence in item c), the phrase should be in item c) to be clear. If antigens "to which an immune response is desired" encompasses any antigen, item c) could be clearly written as --a nucleic acid sequence encoding antigen operatively linked to a promoter--. The phrase "wherein the immunostimulatory

oligonucleotide..." could then be clearly written wherein the --oligonucleotide is not part of the nucleic acid sequence--.

Claim 108 is indefinite because it is unclear if the unmethylated CpG dinucleotide is referring to the unmethylated CpG motif in claim 103 or if the unmethylated CpG dinucleotide is in addition to the unmethylated CpG motif.

Claim 113 is indefinite because the nucleic acid is not administered to the individual or test system in claims 64, 67, 68, 70, 72, 74, 76 or 77. It is unclear if applicants intend the limitation in 113 to refer to the intended use of "to which a nucleic acid encoding an antigen to which an immune response is desired is administered" or if the limitation in claim 113 is setting forth that the nucleic acid is actually being administered.

The phrase "the administration" in claim 113 lacks antecedent basis in claims 64, 67, 68, 70, 72, 74, 76 or 77.

The phrase "within 0-2 days of" (claim 113) is confusing because it is unclear whether the phrase is intended to mean within two days before or two days after administering the immune adjuvant or if it is limited to within two days after administering the immune adjuvant. Use of "0-2" in context does not make sense because it is unclear whether 0 refers to the day of administering the immune adjuvant or some other day.

Claim 115 is indefinite because the limitation cannot be part of claim 113. Administering the nucleic acid before administering the immune adjuvant is not "administering the nucleic acid

within two days of the immune adjuvant" because "within two days of" means administering within two days after the first compound.

Claim Rejections - 35 USC § 102

4. Claims 65, 67, 75 and 76 remain rejected and claims 113-116 are rejected under 35 U.S.C. 102(e) as being anticipated by Urban (6,013,258, Jan 11, 2000) as supported by Krieg (Trends in Microbiology, Jan. 1, 1998, Vol. 6, pages 23-26) for reasons of record.

Urban taught administering a plasmid comprising at least two unmethylated CpG nucleic acid sequence and saponin (ISCOM) (col. 6, line 18). While not relied upon, the inherency of plasmid DNA having unmethylated CpG is supported by Krieg who taught that plasmid DNA is bacterial DNA that has unmethylated CpG (page 23, line 5; page 25, col. 1, p. 1 and 2). Saponin/Quil A is inherently derived from *Quillaja saponaria* and considered "substantially" pure because the term "substantially" is not defined in the specification and because saponin must be purified away from other compounds to be obtained. The peptides and nucleic acids can be delivered with Saponin or separately (col. 6, line 25).

Applicants argue that Urban does not teach an immunostimulatory oligonucleotide having "non-traditional" nucleotides as newly amended. Applicants argument is not persuasive. The metes and bounds of "non-traditional nucleotides" cannot be determined because the phrase is not defined in the specification and does not have an art accepted meaning. In addition, the phrase "non-traditional nucleotides" can be interpreted broadly as encompassing nucleotides having

naturally occurring chemical alterations, e.g. nicked DNA, naturally occurring chemicals that bond to nucleotides. Since the patent office does not have the ability to test whether oligonucleotide of Urban has any "non-traditional" nucleotides as broadly claimed, without evidence to the contrary, the oligonucleotide of Urban has naturally occurring alterations encompassed by "non-traditional" nucleotides. Therefore, Urban anticipates the claims.

5. Claims 65, 67 and 75-77 remain rejected and claims 113-116 are rejected under 35 U.S.C. 102(e) as being anticipated by Sasaki (US Patent 5,808,024, Sept. 15, 1998) as supported by Krieg (Trends in Microbiology, Jan. 1, 1998, Vol. 6, pg 23-26) for reasons of record.

Sasaki taught the pBluescript II SK plasmid encoding an antigen (col. 18, lines 4-19; col. 11, lines 22-45) and combining such plasmids with QS21 (column 3, lines 36-63; see especially lines 39 and 63). pBluescript II SK inherently has at least one unmethylated CpG dinucleotide because plasmids are bacterial DNA which inherently has unmethylated CpG. While not relied upon, the inherency of plasmid DNA having unmethylated CpG is supported by Krieg who states that plasmid DNA is bacterial DNA that has unmethylated CpG (page 23, line 5; page 25, col. 1, p. 1 and 2). QS21 is derived from *Quillaja saponaria* and is "substantially" pure because the term "substantially" is not defined in the specification and because QS21 is a purified saponin.

Applicants arguments regarding Sasaki are the same as those regarding Urban and have been addressed above.

6. Claims 19-20, 24-27, 29-32, 65-68, 73 and 74 remain rejected and claims 90, 91, 95-98, 100-102 and 113-116 are rejected under 35 U.S.C. 102(e) as being anticipated by Agrawal (US Patent 5,968,909, Oct. 19, 1999) for reasons of record.

Agrawal taught a composition comprising a phosphorothoiated oligonucleotide comprising at least two unmethylated CpG nucleic acid sequences and saponin (col. 8, line 29; col. 17, line 27, SEQ ID NO:6; col. 6, line 29). Saponin is inherently derived from *Quillaja saponaria* (claims 20 and 50). Note the "TCGT" and TCGC" sequences within SEQ ID NO:6 which is equivalent to the formula in claims 27 and 57. Agrawal also taught combining the oligos with phospholipids (claims 86 and 89; see col. 6, line 269). The phrase "for increasing the immune response to an antigen in an individual or a test system to which the antigen is administering" (claims 67, 68, 74) is an intended use and does not bear patentable weight because it may not occur. As written, claims 67, 68, 74 and those dependent therefrom merely require administering the composition. Thus, Agrawal anticipates the claims.

Applicants argue Agrawal does not teach the method claimed because it results in reducing the immunostimulatory effect of the oligonucleotides. Applicants arguement is not persuasive because immunostimulation still occurs. Applicants argue Agrawal does not teach saponin is "immunostimulatory" as newly amended. Applicants arguement is not persuasive because Agrawal taught obtaining an immune response. In addition, the distinction between a "saponin adjuvant" and a "saponin immunostimulatory adjuvant" cannot be determined (see 112/2nd over "saponin immunostimulatory adjuvant"). Applicants argue Agrawal requires using

saponin in a liposome or mice; however, applicants argue not all saponins that form liposomes or micelles have antigenic activity. Without evidence to the contrary, the saponin of Agrawal is inherently "immunostimulatory" because an immune response is obtained. The point of Agrawal is to reduce the immune response by adding phosphorothioate to the oligonucleotides being delivered using any lipid commonly used in the art, including saponin. Therefore, the teachings of Agrawal are not limited to using non-immunostimulatory saponin. As such, Agrawal teaches a "saponin immunostimulatory adjuvant" as claimed.

Claim Rejections - 35 USC § 103

7. Claims 19-27, 63-68, 73-77 and 80-83 remain rejected and claims 90, 91, 95-98, 100-102 and 113-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner (Sept. 1997, PNAS, Vol. 94, pages 10833-10837) in view of Kensil (1996, Critical Reviews in Therapeutic Drug carrier Systems, Vol. 13, No. 1 and 2, pages 1-55) for reasons of record.

Weiner taught administering oligonucleotide 1643 increased the humoral immune response in a mouse (page 10834, col. 1). 1643 has three unmethylated CpG motifs (Table 1, page 10834). Note the "ACGC" "TCGA" and "TCGA" which are equivalent to the formula in claims 27 and 57. 1643 is phosphorothioated (page 10833, col. 2, 11 lines from the bottom) (claims 25, 26, 55, 56 and 65-68). Weiner does not teach combining 1643 with QS-7, -17, -18 or -21. However, at the time of filing, Kensil taught combining QS-7, -17, -18 or -21 with other adjuvants to increase

the adjuvant effect (page 6, line and page 23). QS-7, -17, -18 and -21 are purified from saponin which is purified from *Quillaja saponaria* (page 3).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine oligonucleotide 1643 of Weiner with QS-7, -17, -18 or -21 as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Weiner and Kensil are directed toward compositions with adjuvants that increased the humoral immune response and 2) 1643 and QS-7, -17, -18 or -21 could be combined because it was common for one of ordinary skill in the art at the time of filing to combine adjuvants to increase the humoral immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to combine oligonucleotide 1643 and QS-7, -17, -18 or -21 to increase the humoral immune response.

Claims 80-83 are included because the composition taught by the combined teachings of Weiner and Kensil would cause an immune response. It is noted that the claims do not require administering an antigen and the phrase "when administered to an individual" is not limited to when an antigen is administered to an individual; it could also mean when the two adjuvants are administered to an individual. Overall, the phrase in claim 80 does not add a functional limitation that distinguishes the composition claimed from the composition of Weiner and Kensil.

Applicants argue new oligonuceotide 2006 shows synergy in combination with QS-21. Applicants arguement is not persuasive. The claims are not limited to using oligonucleotide 2006 and QS-21 or to an immunostimulatory activity that is distinguishable from that of the combined

teachings of Weiner and Kensil. Nor are the claims limited to a reasonable scope of oligos that correlate to the oligos that show synergy, i.e. the broad claims encompass any nucleic acid having unmethylated CpG. In addition, oligonuceotide 2006 was not available at the time of filing. Applicants discussion on pg 15-16 regarding types of saponin and synergy are moot because Kensil taught the species of saponin claimed. In addition, the claims are not limited to the species of saponin that had synergistic immunostimulatory activity or to an immunostimulatory activity that is distinguishable from that of the combined teachings of Weiner and Kensil.

8. Claims 19-21, 24, 25, 27-32, 65, 67, 69, 60, 73-77 and 80-83 remain rejected and claims 90, 91, 95-98, 100-102 and 113-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weiner (Sept. 1997, PNAS, Vol. 94, pages 10833-10837) in view of Kensil (1996, Critical Reviews in Therapeutic Drug carrier Systems, Vol. 13, No. 1 and 2, pages 1-55) for reasons of record.

Weiner taught administering oligonucleotide 1758 increased the humoral immune response in a mouse (page 10834, col. 1) which has an unmethylated CpG motifs and is equivalent to SEQ ID NO:1. 1758 is phosphorothioated (page 10833, col. 2, 11 lines from the bottom) (claims 25, 26, 55, 56 and 65-68). Weiner does not teach combining 1758 with Quil A. However, at the time of filing, Kensil taught combining Quil A with other adjuvants to increase the adjuvant effect (page 6, line and page 23). Quil A is purified from *Quillaja saponaria,* is less purified than QS-7, 17, 18 or -21 and has less of an adjuvant effect than QS-7, 17, 18 or -21 (page 3, page 5, Fig. 1, page 11).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine oligonucleotide 1759 of Weiner with Quil A as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Weiner and Kensil are directed toward compositions with adjuvants that increase the immune response and 2) 1758 and Quil A could be combined because it was common for one of ordinary skill in the art at the time of filing to combine adjuvants to increase the immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to combine oligonucleotide 1758 and Quil A to increase the immune response.

Applicants arguments are addressed above.

9. Claims 19-27, 63-68, 71-78 and 80-83 remain rejected and claims 90, 91, 95-98, 100-102 and 113-116 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chu (Nov. 17, 1997, J. Exp. Med., Vol. 186, pg 1623-1631) in view of Kensil (Kensil, 1996, Critical Reviews in Therapeutic Drug Carrier Systems, Vol. 13, No. 1 and 2, pg 1-55) for reasons of record.

Chu taught administering oligonucleotide 1826 or 1760 as an adjuvant increased the IgG2a immune response in a mouse (pg 1625, col. 2, Fig. 1A and 1D). 1826 and 1760 have unmethylated CpG motifs and 1826 is equivalent to SEQ ID NO:2. 1826 and 1760 are phosphorothioated (page 1625, col. 1, Table 1) (claims 25, 26, 55, 56 and 65-68). Chu did not teach combining 1826 or 1760 with Quil A, QS-7, -17, -18 or -21. However, Kensil taught combining Quil A, QS-7, -17, -18 or -21 with other adjuvants to increase the adjuvant effect (page 6, line and page 23). Quil A is purified from *Quillaja saponaria,* and QS-7, 17, 18 and -21

are purified from a less pure formulation of saponin. Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine oligonucleotides 1826 or 1760 of Chu with Quil A, QS-7, 17, 18 or -21 as taught by Kensil. One of ordinary skill in the art at the time the invention was made would have recognized that 1) both Chu and Kensil are directed toward compositions with adjuvants that increase the immune response and 2) 1826 or 1760 and Quil A, QS-7, 17, 18 or -21 could be combined because it was common for one of ordinary skill in the art at the time of filing to combine adjuvants to increase the immune response. One of ordinary skill in the art at the time the invention was made would have been motivated to add oligonucleotide 1826 or 1760 and Quil A, QS-7, 17, 18 or -21 to increase the IgG2a immune response.

Applicants have shown unexpected results with the specific combination of QS-21 and phosphorothioated oligonucleotide 1826. Applicants argument would be persuasive if the claims were limited to the combination of QS-21 and 1826. Furthermore, it is unclear whether 1760 has an equivalent adjuvant effect because the effect of nucleic acid sequences comprising unmethylated CpG motifs varies (page 9, first full paragraph of the instant application). Therefore, it is unclear whether 1760 has an equivalent adjuvant effect as 1758 or 1826. In addition, the adjuvant effect of Quil A is not equivalent to the adjuvant of QS-7, -17, -18 and -21 (Kensil, pg 11, para. 1 and 2). In conclusion, it is not clear that the combination of 1760 and Quil A, QS-7, 17, 18 or -21 would have the same unexpected results as 1758 or 1826 and QS-21.

Applicants arguments regarding Chu in view of Kensil appear to be combined with the arguments regarding Weiner in view of Kensil which are addressed above.

The limitation of a CpG motif having the formula 5'$X_1CGX_2$3' in claim 27, 98 and 111 cannot be adequately searched on computer databases because the nucleic acid is so small and may be part of a plasmid which is very large. The formula has been found in the references of record, but cannot be searched alone or in combination with saponin.

Conclusion

No claim is allowed.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-0120.

Questions of formal matters can be directed to the patent analyst, Dianiece Jacobs, who can normally be reached on Monday through Friday from 9:00 am to 5:30 pm at (703) 305-3388.

Questions of a general nature relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-1235.

If attempts to reach the examiner, patent analyst or Group receptionist are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051.

The official fax number for this Group is (703) 308-4242.

Michael C. Wilson

MICHAEL C. WILSON
PATENT EXAMINER